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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Dalacin® / Clindamycin phosphate

PROTOCOL NO.: M11000093

PROTOCOL TITLE: Comparative Evaluation of Clindamycin vs Clindamycin Plus Tobramycin in the Treatment of Pelvic Inflammatory Disease

Study Centre: Study was conducted at 1 centre in the United States.

Study Initiation Date and Completion Date: Information not available (Study report approved on 08 August 1988).

Phase of Development: Phase 4

Study Objective: To evaluate clindamycin as a single-antibiotic therapy (compared with clindamycin-tobramycin combination therapy) in women with acute pelvic inflammatory disease (PID) or acute salpingitis who required in-patient parenteral antimicrobial therapy.

METHODS

Study Design: This was a randomised, double-blind, prospective study to compare clindamycin plus clindamycin plus tobramycin in the parenteral treatment of hospitalised women with acute PID or acute salpingitis. Eligible female subjects were enrolled and randomized to receive either clindamycin plus placebo or clindamycin plus tobramycin intravenous (IV) therapy for 4 days, followed by oral (PO) clindamycin therapy for 14 days. Hospital discharge examination included repeat cervical and endometrial cultures for subjects with positive baseline culture. A follow-up examination was performed for all subjects at 2-6 weeks after hospital discharge. Subjects with positive admission endometrial and cervical cultures were recultured for Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum and Neisseria gonorrhoeae at this follow-up visit. Subjects with positive admission cultures for C. trachomatis were asked to return for an additional follow up culture at 21-35 days after the end of protocol therapy.

Number of Subjects (Planned and Analysed): A total of 59 subjects were enrolled, and 51 subjects were treated and analysed for efficacy.

Diagnosis and Main Criteria for Inclusion: Female subjects of above 15 years of age, not allergic to any of the study drugs, and with clinical evidence of acute PID were enrolled in the study. Physical findings required for the diagnosis were direct abdominal tenderness with or without rebound, cervical motion tenderness, fundal tenderness, and adnexal tenderness.
In addition, at least 1 of the following conditions had to be met for the subject to be eligible for the study: 1) gram negative intracellular diplococci identified on gram stain of endocervical specimen; 2) admission temperature greater than 38°C; 3) admission white blood cell count (WBC) greater than 10,000/mm$^3$; 4) purulent material from peritoneal cavity by laparoscopy or culdocentesis; or 5) pelvic abscess or inflammatory complex on bimanual exam or by sonography.

**Study Treatment:** Clindamycin 900 mg every 8 hours (q8h) plus tobramycin 80 mg/m$^2$ q8h was administered IV for a minimum of 4 days for subjects randomized to that treatment schedule. For those on clindamycin alone, the same dose of clindamycin was given with a placebo for tobramycin for at least 4 days. In both groups, at the end of IV therapy, oral clindamycin 450 mg taken every 6 hours (q6h) was prescribed to complete 14 days of treatment. Serum concentrations of tobramycin were monitored during the study, and dosage adjustment was made as required.

**Efficacy Evaluations:** Efficacy was evaluated based on clinical outcome, defined as success or failure, where failure was defined as persistence or worsening of signs and symptoms during the first 48 hours of treatment, initial improvement and then worsening during protocol treatment, protocol treatment required beyond 14 days, or additional antibiotics required to treat protocol-related infection. Bacteriologic responses in the subjects were assessed prior to treatment by urine sample culture and cervical cultures (for *N. gonorrhoeae*, *C. trachomatis*, *M. hominis* and *U. Urealyticum*) and endometrial specimens (for *C. trachomatis*, *M. hominis* and *U. Urealyticum*). Peritoneal fluid obtained at laparoscopy or culdocentesis was cultured for aerobes and anaerobes.

**Safety Evaluations:** Safety was evaluated by monitoring adverse events (AEs) and serious adverse events (SAEs). Haematologic renal and liver function tests were monitored prior to, during, and after the therapy.

**Statistical Methods:** Descriptive statistics approach was used to compare the 2 treatments. Comparison was done by number of successful cases in the 2 treatment groups. Also the bacteriologic response in subjects with positive *N. gonorrhoeae*, *C. trachomatis*, *M. hominis* and *U. urealyticum* cultures were compared using descriptive statistics.

**RESULTS**

**Subject Disposition and Demography:** A total of 59 subjects were enrolled into the trial, 8 of which were deemed nonevaluable for analysis of efficacy. Of the 51 evaluable subjects, 28 received clindamycin plus tobramycin, and 23 were treated with clindamycin alone.

Of the 8 nonevaluable cases, 3 were found to have acute pyelonephritis; 1 subject elected to withdraw from the study prior to receiving any protocol medication; 1 signed out of the hospital after 24 hours of treatment; 2 subjects received additional non-protocol antibiotics; and 1 subject received <48 hours of protocol therapy.

Demographic data of these subjects is shown in Table 1. Age, intra uterine device (IUD) use, previous PID, and previous sexually transmitted disease (STD) were statistically similar in both groups. The mean age was 25 years with a range of 15 to 43 years. Eight subjects from
each group reported IUD use with a duration of use ranging from 6 to 60 months. The number of previous PID episodes experienced ranged from 0 to 6, and 61% in each group were reported none. The number of previous STD infections reported ranged from 0 to 4 and 71% in the clindamycin/tobramycin group and 61% in the clindamycin group reported none.

Table 1. Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Clindamycin/Tobramycin</th>
<th>Clindamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in years)</td>
<td>26.1</td>
<td>23.8</td>
</tr>
<tr>
<td>IUD use (%)</td>
<td>28.6</td>
<td>34.8</td>
</tr>
<tr>
<td>Previous PID (%)</td>
<td>39.0</td>
<td>39.0</td>
</tr>
<tr>
<td>Previous STD infections (%)</td>
<td>28.6</td>
<td>39.1</td>
</tr>
</tbody>
</table>

IUD=Intra uterine device; n=Number of subjects; PID=Pelvic inflammatory disease; STD=Sexually transmitted disease.

Infection variables at admission were also similar in each regimen: the mean leucocyte count prior to therapy was 14.9 and 13.4 for clindamycin/tobramycin and clindamycin, respectively. At study entry, 19/28 (68%) of those in the clindamycin/tobramycin group and 13/23 (57%) in the clindamycin series had a temperature <100.4°F. The number of days of IV therapy ranged from 4 to 9 days, with a mean of 5.2 for the clindamycin/tobramycin subjects and 4.8 for those in the clindamycin group were not significantly different (p=0.36).

Efficacy Results:

1. Clinical outcome is presented in Table 2.

Table 2. Overall Results of Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clindamycin/Tobramycin</th>
<th>Clindamycin</th>
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</thead>
<tbody>
<tr>
<td>Success</td>
<td>27/28 (96%)</td>
<td>20/23 (87%)</td>
</tr>
<tr>
<td>Failure</td>
<td>1/28 (4%)</td>
<td>3/23 (13%)</td>
</tr>
</tbody>
</table>

Failures in the clindamycin group (3 subjects): One failure reported in the clindamycin group was a 30-year old subject admitted with an acute exacerbation of chronic PID. In addition to abdominal and pelvic organ tenderness, she had WBC of 10200/mm³, oral temperature of 100.4°F, and purulent material was present in the pelvic cavity on laparoscopy. Both _N. gonorrhoeae_ and _C. trachomatis_ cultures were negative on admission; however, endometrial cultures for _M. hominis_ and _U. urealyticum_ were positive. After 5 days of IV therapy with the study drug, she continued to have abdominal and rebound tenderness accompanied by low grade fever. Triple antibiotic therapy was then initiated with symptoms of pain decreasing after 2 days. The subject was completely asymptomatic at follow-up 2 weeks after discharge.

A second failure in the clindamycin treatment group was considered a clinical success but did require ceftriaxone at the time of the first follow-up visit for treatment of persistently positive _N. gonorrhoeae_ culture.
The third failure in the clindamycin group was readmitted to the hospital 12 days after the original admission with PID symptoms and required additional therapy.

Failure in the clindamycin/tobramycin group (1 subject): The single failure in the clindamycin/tobramycin series was judged an initial clinical success; however, her baseline culture for both *N. gonorrhoeae* and *C. trachomatis* remained positive at follow-up examination and she was readmitted with recurrent PID and required definitive surgical treatment for cure.

Other clinically relevant findings:

For those subjects with temperature >100.4°F on admission, 9/28 (32%) for those in the clindamycin/tobramycin group, and 10/23 (43%) for those in the clindamycin series, a range of 4 to 60 hours was required for defervescence. There were no significant differences between the treatment groups in the distribution of subjects into the collapsed categories 1 to 5 hours, 6 to 10 hours, and >10 hours.

Pelvic pain was present in all but 1 subject at baseline. Rapid improvement was noted in both treatment groups from day to day following baseline with no statistically significant differences noted. In an assessment of abdominal tenderness, it was noted that by Day 4, 89% of subjects in the clindamycin/tobramycin group and 95% of those treated with clindamycin were classified as improved.

2. Bacteriologic response:

Pre-therapy recovery of *N. gonorrhoeae*, *C. trachomatis*, *M. hominis*, and *U. urealyticum* is displayed in Table 3.

**Table 3. Recovery of Organisms from 51 Subjects.**

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Clindamycin/Tobramycin</th>
<th>Clindamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cervix</td>
<td>Endometrial</td>
</tr>
<tr>
<td><em>N. gonorrhoeae</em></td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td><em>C. trachomatis</em></td>
<td>5</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>M. hominis</em></td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td><em>U. urealyticum</em></td>
<td>17</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Cervical culture negative; <sup>b</sup> Both cervical cultures and endometrial cultures positive

*C. trachomatis* was isolated from a total of 15 of the evaluable cases; 6 in the clindamycin/tobramycin group and 9 in those treated with clindamycin alone. In 13 of the 15 subjects, test of cure cultures were all negative; however, in 2 cases, the subject did not return for the late follow-up visits. In 1 case, who was treated with clindamycin alone, the culture for *C. trachomatis* remained positive at time of hospital discharge but was negative at the 2 week follow-up. This subject was readmitted 8 days after hospital discharge, however, with an acute exacerbation of PID and required additional antibiotic therapy. A second subject had a persistent positive chlamydial culture at 3 weeks with negative culture at 6 weeks. This case had received clindamycin/ tobramycin treatment and was readmitted to the hospital at 7 weeks after her original admission with an exacerbation of PID and...
subsequently underwent hysterectomy and unilateral salpingo-oopherectomy for chronic PID.

*N. gonorrhoeae* was cultured from cervical samples in 15 subjects and from endometrial sampling in one. One additional subject had negative cultures for *N. gonorrhoeae* but had gram negative diplococci found on examination of cervical sampling. Of the 17 cases thus described, 8 were in the clindamycin/ tobramycin group and 9 in the group which received clindamycin alone. Of these with positive cervical cultures on admission (same 15 cases), 12 were culture negative at discharge from the hospital and at follow-up. One case in the clindamycin group responded clinically but had persistent *N. gonorrhoeae* cultures and was treated with ceftriaxone after discharge. Another case in the clindamycin/tobramycin group was culture negative at discharge but was found to be positive at follow-up and was readmitted for recurrent PID. The third case was culture negative at discharge but positive at follow-up. The investigator considered this subject a success with reinfection. One subject had a positive endometrial culture reported prior to therapy and was treated with clindamycin alone; this case responded satisfactorily to treatment and had negative discharge cervical *N. gonorrhoeae* cultures but was lost to follow-up. One subject in the clindamycin/tobramycin group had a positive gram stain for gram negative diplococci but negative cultures; she was treated in the clindamycin/tobramycin group and was a clinical success.

Pre-therapy cervical cultures for *M. hominis* were positive in 14 (13 cervical and 1 endometrial) subjects treated with clindamycin/tobramycin and in 17 of those in the clindamycin group. This organism was eradicated at follow-up in 47% of those in the clindamycin/tobramycin series and 68% in those receiving clindamycin alone which was not a statistically significant difference.

*U. urealyticum* was present in 17 subjects in the clindamycin/tobramycin group and in 19 of those in the clindamycin alone regimen at baseline. At follow-up, only 1 of those subjects who tested positive at baseline had a negative culture. No significant difference between the 2 groups was detected.

**Safety Results:**

Ten subjects in this investigation reported side effects. One subject on clindamycin/tobramycin reported both diarrhoea and a macular rash. She had oral therapy discontinued after 8 days of oral treatment although she was considered a satisfactory response. The remaining 9 subjects had diarrhoea only reported as a side effect and in none of these cases was the adverse reaction of such severity as to require discontinuation of protocol therapy. Three of the 9 subjects were in the clindamycin treatment group; all were of a single day's duration, 2 of which were not considered a drug-related side effect by the investigator and 1 was noted on the first day of resumption of general diet. Six of the 9 cases were in subjects who received both clindamycin and tobramycin. Five of the cases were reported as transient loose stools on a single day of treatment and were not considered clinically significant. One subject experienced between 3 and 6 loose stools per day for the first 3 days of protocol therapy; medication was continued and the diarrhoea subsided without additional treatment and the subject was a clinical success.
CONCLUSIONS: Clindamycin appeared to be active against *C. trachomatis* in this trial. It is noted that aminoglycosides have little in vitro activity against this organism, whereas previous observations have suggested that parenteral clindamycin may be effective treatment in vivo for infection. Overall, *C. trachomatis* was isolated from 15/51 (29%) of the cases, and test of cure follow-up cultures were negative in 13/15 (87%). These findings are highly suggestive that *C. trachomatis* had been eliminated in these subjects rather than merely suppressed, and support the hypothesis that clindamycin is effective in vivo for treatment of PID providing adequate coverage for the *C. trachomatis* component of the infection.